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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,487	02/10/2004	Denise L. Faustman	00786/457003	1044

21559 7590 10/08/2008

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/775,487	FAUSTMAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-78* is/are pending in the application.

4a) Of the above claim(s) *78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-24-07 9-17-07 7-2-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 2, 2008 has been entered.

   Claims 1-75 and 79-82 have been canceled.

   Claims 76-78 have been amended.

   Claims 76-78 are pending.

2. Applicant requests that claim 78 be rejoined and examined pursuant to 37 C.F.R. § 1.104. Applicant's request is denied as claim 78 is drawn to a non-elected invention (see the previous Restriction Requirement mailed February 28, 2006). Furthermore, the examiner has considered 37 C.F.R. § 1.104 and does not understand how it is relevant to applicant's request for rejoinder.

   Thus, claims 76 and 77 are under examination as they read on a method of treating a human exhibiting symptoms of an autoimmune disease selected from the group consisting of diabetes, lupus erythematosis, rheumatoid arthritis, multiple sclerosis, scleroderma, Crohn's disease, Grave's disease, psoriasis, Celiac disease, adult-onset idiopathic hypoparathyroidism (AOIH), Sjogren's syndrome, and Addison's disease, said method comprising administering to said human mammal a therapeutically effective amount of an agent that binds to a cell-surface receptor, thereby activating the NFkB signaling pathway, wherein the elected species of autoimmune disease to be treated is "diabetes".

   Moreover, claim 78 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 30, 2006.

3. The previous rejection under 35 U.S.C. § 112, 1st paragraph has been withdrawn upon consideration of applicant's remarks and the post-filing date evidence of Ban et. al. submitted with applicant's remarks filed July 2, 2008.

   The previous rejection under 35 U.S.C. § 102(b) has been withdrawn in view of applicant's amendment to the claims to recite treating a "human".

   New Grounds of Rejection are set forth below.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 76 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 76 recites a method of treating a human exhibiting symptoms of an autoimmune disease selected from the group consisting of diabetes, lupus erythematosis, rheumatoid arthritis, multiple sclerosis, scleroderma, Crohn's disease, Grave's disease, psoriasis, Celiac disease, adult-onset idiopathic hypoparathyroidism (AOIH), Sjogren's syndrome, and Addison's disease, said method comprising administering to said human mammal a therapeutically effective amount of ***an agent that binds to a cell-surface receptor***, thereby activating the NFkB signaling pathway.

Applicant indicates on page 3 of their Remarks filed July 2, 2008 that the instant claims are supported by the disclosure of the instant specification and prior claims 79 and 80.

However, none of the sections of the instant specification applicant points to or the prior claims provide sufficient written description support for "a method of treating a human exhibiting symptoms of an autoimmune disease selected from the group consisting of diabetes…comprising administering…***an agent*** ***that binds to a cell-surface receptor***, thereby activating the NFkB signaling pathway."

Previously pending claims 76 and 79 read upon a method of treating a human mammal having, or predisposed to having, an autoimmune disease, said method comprising administering to said human mammal a therapeutically effective amount of a substance that stimulates a signaling pathway that activates NFkB.

Thus, previously pending claims 76 and 79 were generic to currently pending claim 76 which recites "an agent that binds to a cell-surface receptor, thereby activating the NFkB signaling pathway."

The instant specification discloses methods of treatment comprising administering a variety of protein agents which restores NFKB activity in an amount and for a time sufficient to result in normal NFKB activity in the mammal, wherein said protein agents are various cytokines and cell adhesion molecules such as tumor necrosis factor-α, E-selectin, I-cam, V-cam, interleukin-2, interleukin-6, granulocyte colony-stimulating factor, interferon-β (see instant specification page 21, last paragraph) and IL-1 (see instant specification page 53, 2nd

paragraph). At least some of these factors are known to bind to a cell-surface receptor, thereby activating the NFkB signaling pathway (see, ibid).

However, applicant is now claiming a subgenus not sufficiently supported by the specification as-filed.

The specification does not appear to provide blazemarks nor direction for the limitation "***an agent that binds to a cell-surface receptor***, thereby activating the NFkB signaling pathway".

The instant claims recite a limitation which was not clearly disclosed in the specification as-filed, and changes the scope of the instant disclosure as-filed. Such a limitation recited in the instant claim, which did not appear in the specification as filed, introduces a new concept and violates the description requirement of the first paragraph of 35 U.S.C. 112.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant should indicate in detail how the instant specification provides written support for the claimed limitation. See MPEP 714.02 and 2163.06.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 76 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, ***while being enabling for***

a method of treating a human exhibiting symptoms of insulin dependent diabetes mellitus, said method comprising administering to said human a therapeutically effective amount of TNF-α, thereby activating the NFkB signaling pathway,

does not reasonably provide enablement for

a method of treating a human exhibiting symptoms of an autoimmune disease selected from the group consisting of diabetes, lupus erythematosis, rheumatoid arthritis, multiple sclerosis, scleroderma, Crohn's disease. Grave's disease, psoriasis, Celiac disease, adult-onset idiopathic hypoparathyroidism (AOIH). Sjogren's syndrome, and Addison's disease, said method comprising administering to said human mammal a therapeutically effective amount

of an agent that binds to a cell-surface receptor, thereby activating the NFkB signaling pathway, such as TNF-α.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method of treating a human exhibiting symptoms of an autoimmune disease selected from the group consisting of diabetes, lupus erthematosis, rheumatoid arthritis, multiple sclerosis…said method comprising administering to said human mammal a therapeutically effective amount of an agent that binds to a cell-surface receptor, thereby activating the NFkB signaling pathway, such as TNF-α.

In the interest of compact prosecution, assuming that the claims as amended do not constitute new matter as asserted in Section 5 above, the instant claims, given their broadest reasonable interpretation consistent with the instant specification, read on methods of treatment comprising administering a variety of "agents" that bind to a cell-surface receptor, thereby activating the NFkB signaling pathway. These "agents" include various nucleic acids, organic chemicals (see instant specification page 19, 3rd paragraph), various cytokines and cell adhesion molecules such as tumor necrosis factor-α, E-selectin, I-cam, V-cam, interleukin-2, interleukin-6, granulocyte colony-stimulating factor, interferon-β (see instant specification page 21, last paragraph) and IL-1 (see instant specification page 53, 2nd paragraph).

While the claims may recite that the administered agents bind to a cell-surface receptor, thereby activating the NFkB signaling pathway, consistent with applicant's arguments and post-filing date art concerning enablement of the claimed invention under 35 U.S.C. § 112,1st paragraph, the effectiveness of the claimed invention is not dependent on NFkB activity, *per se*, but ***on a different signaling pathway*** that is activated by the same agent that binds to a cell-surface receptor, thereby activating the NFkB signaling pathway, ***said different signaling pathway inducing apoptosis*** of CD8+ T cells in NOD mice. (see applicant Remarks filed July 2, 2008 pages 5-10).

However, neither the instant specification nor the prior art provide sufficient guidance or direction for one of ordinary skill in the art to make and/or use the multitude of agents encompassed in the breadth of the claimed invention to bind to a cell-surface receptor, thereby activating the NFkB signaling pathway, wherein the end result is apoptosis.

With respect to using nucleic acids and "organic molecules" to bind to a cell-surface receptor, thereby activating the NFkB signaling pathway, wherein the end result is apoptosis, the skilled artisan would to very unclear as to how to go about using the former for this purpose and while the skilled artisan may be able to envision an organic chemical binding to a cell-surface receptor and activating NFkB, the instant specification provides no guidance or direction as to how to make such a chemical or what cell-surface receptor such a molecule should bind.

Apart from showing that spleen cells obtained from NOD mice undergo apoptosis when stimulated with TNF-α as compared to wild type cells as a consequence of defect in the NOD mice spleen cell in producing the "active" signaling form of NFKB due a defect in the NOD mouse proteosome (see instant specification page 124, lines 20-22; page 126, line 5 through page 127, line 6 and Figures 13A-13D), the instant specification gives no guidance or direction as to the particular conditions under which, if any at all, the various cytokines and cell adhesion molecules that bind to a cell-surface receptor, thereby activating the NFkB signaling pathway, such as tumor necrosis factor-α, E-selectin, I-cam, V-cam, interleukin-2, interleukin-6, granulocyte colony-stimulating factor, interferon-β and IL-1 can also activate a different signaling pathway that induces CD8+ T cell apoptosis.

Moreover, the skilled artisan, as of applicant's date of invention recognized that, in general, many of the cytokines recited in the instant specification induce T cell proliferation and are in fact antiapoptotic in many cases. For example consider Fukada et al., Immunity. 1996 Nov;5(5):449-60, which teaches that IL-2, IL-6 and many other cytokines signaling through gp130, well known in the art as the cytokine receptor "common signaling chain," induce STAT3 signaling which induces anti-apoptotic genes such as bcl-2 (see Fukada introduction Section pages 449-450; page 453, right column and page 457).

Likewise, the skilled artisan would have little reason to believe that granulocyte colony-stimulating factor would be able to induce an apoptosis signal for CD8+ T cells given that it mediates antiapoptotic signaling in neutophils (see Gottlieb et al., Proc Natl Acad Sci U S A. 1995 Jun 20;92(13):5965-8, Abstract).

Similarly, a comprehensive review of IL-1 published around applicant's date of invention emphasizes the potent inflammatory activity of this molecule and only discusses apoptosis in the context of the IL-1β converting enzyme (ICE, a.k.a. caspase-1) which is required for IL-1 activation not in the context of IL-1 induced CD8+ T cell death (see Dinarello et al., Int Rev Immunol. 1998;16(5-6):457-99, pages 9-14).

With respect to administering an agent that binds to a cell-surface receptor, thereby activating the NFkB signaling pathway to treat the human autoimmune diseases with diverse etiologies recited in the instant claims, their is substantial knowledge in the art that *inhibition* of one such agent, TNF-α, is beneficial in treatment of autoimmune diseases.

For example Mariott et al. (Exp. Opin. Invest. Drugs, 1997, Vol. 6, p. 1105-1108, cited on an IDS) have shown that inhibition of TNF-alpha was successfully used to treat rheumatoid arthritis and Crohn's disease in human clinical trials.

Similarly, Le et al. (US Patent 5,919,452) discloses and claims methods of treating a variety of autoimmune disease, including some recited in the instant claims, comprising administering anti-TNFα antibody to a human patient (see claims 1-12, and column 34, lines 14-19).

Moreover some of the beneficial effects of inhibiting TNFα are independent of its direct pro-inflammatory effects on T cells. For example, Almonte et al. (Clin Rheumatol. 1992 Jun;11(2):202-5, cited on an IDS) teaches that TNF-α can induce the production of IL-1b, and that both molecules can act locally to induce bone and cartilage resorption, synoviocyte proliferation and the production of prostaglandins and proteases that amplify the destructive process in the joint (see, for example, Introduction, in particular page 202) – certainly not something that would lead to treatment of a rheumatoid arthritis or lupus patients who often has overlapping symptoms with the RA patient and furthermore not something that can be avoided even if the TNFα were to kill autoreactive CD8+ T cells.

Various post-filing date publications from the laboratory of Dr. Faustman, and the draft manuscript of Ban et al. submitted with applicant's remarks filed July 2, 2008 teaches apoptosis of autoimmune T cells in NOD mice and reversal of autoimmune diabetes in NOD mice due to treatment with TNF-alpha, see for example Kodama et al., Cell Mol Life Sci. 2005 Aug;62(16):1850-62, cited on an IDS, which is a review of the subject. These publications describe rationales for how administering TNF-alpha could be beneficial in the treatment of a variety of autoimmune diseases.

Thus there are contradictory teachings in the art with regard to treating autoimmune diseases with TNF-alpha antagonists versus treating autoimmune diseases with TNF-alpha agonists.

Applicant's response filed July 2, 2008 includes argument and scientific data allegedly demonstrating that the claimed invention is enabled. Many of these arguments point to post-filing date art further investigating the mechanism and effectiveness of TNFα treatment of NOD mice and discussing the rationales, but providing no direct experimental support for the use of TNF-α treatment for the variety of other autoimmune diseases recited in the instant claims.

However, the Ban draft manuscript submitted with applicant's remarks and amendment filed June 20, 2007 does present convincing data based on CD8+ T cells isolated from humans with established type I diabetes.

With respect to diseases other than IDDM, in the supplemental data section of their draft manuscript Ban shows that either one, and for some, possibly two samples of isolated CD8+ peripheral blood lymphocytes from a lupus patient(s?), a psoriasis patient(s?), a multiple sclerosis patient(s?), a hypothyroidism patient, a Crohn's patient, and a Grave's disease patient were tested for their sensitivity to TNFα treatment as compared to normal controls (the (s?) is because it is unclear from the draft manuscript if one sample was tested under two conditions or if two independent samples were tested under two conditions in Supplemental Figures S2 and S4).

However, this Ban data does not convincingly establish that the claimed method could be used to treat a patient exhibiting symptoms of generic "diabetes" or the variety of autoimmune diseases recited in the instant claims for a variety of reasons.

In contrast to the data reported for IDDM patients in the non-supplemental part of the Ban draft manuscript, Supplemental Figures S2 and S4 report results for 1-2 patients, not a plurality of IDDM patients which allowed for statistically significant results to be achieved as reported in the non-supplemental part of the Ban draft manuscript on page 8, 2nd paragraph.

Furthermore, unlike the data for IDDM patients, there is no evidence in the Ban draft manuscript that the CD8+ T cells being killed by TNFα in the various non-IDDM autoimmune diseases are cells that would be expected to contribute to lupus erythematosis, rheumatoid arthritis, multiple sclerosis, scleroderma, Crohn's disease, Grave's disease, psoriasis, Celiac disease, adult-onset idiopathic hypoparathyroidism (AOIH), Sjogren's syndrome, or Addison's disease pathogenesis.

Another distinction between the IDDM patients and the other patients whose isolated CD8+ peripheral blood lymphocytes were tested is that according to Ban Supplemental Information page 1, 2nd paragraph: "All type 1 diabetic patients were in good health, not in renal failure, had neither received kidney transplants nor systemic immunosuppressive therapy, and had longstanding disease of at least 4-years duration. All other autoimmune patients were on standard therapy regimens for their particular disease."

Thus, the "other autoimmune patients" were exposed to whatever immunosuppressants/other drugs which are normally administered to treat their various diseases. It is quite possible that exposure of these other autoimmune patients to these immunosuppressants/other drugs could confound the response of their isolated CD8+ peripheral blood lymphocytes to TNFα and/or the evaluation of cell death/proliferation via lactate dehydrogenase release due to membrane permeability.

For example, the immunosuppressive antiproliferative agent methotrexate commonly used in the treatment of variety of autoimmune diseases sensitizes naïve T cells to activation induced apoptosis (see Genestier et al., J Clin Invest. 1998 Jul 15;102(2):322-8, in particular page 326, right column, 1st paragraph).

Likewise, methotrexate also inhibits lactate dehydrogenase enzymatic activity, and this inhibition by all indications is a direct effect on the enzyme (see, e.g., Rabb et al., Arch Dermatol Res. 1975 Aug 29;253(1):77-84, in particular, page 82 and Figure 4 and Caetano et al., Cell Biochem Funct. 1997 Dec;15(4):259-64, in particular Introduction on pages 259-260).

While it is acknowledged that the experiments of Ban include a "no TNFα control" from the disease patient to account for TNFα independent decreases in lactate dehydrogenase enzymatic activity, if the absolute values of lactate dehydrogenase enzymatic activity in both the control and test samples are lower than, for example, in samples obtained from patients treated with methotrexate, this could lead to uncertainty of the measurement as small signals are well known in the art to be less reliable.

Furthermore, the various autoimmune diseases encompassed in the breadth of the instant claims have diverse etiologies and mechanisms of pathogenesis. While the NOD mouse is a model of an animal predisposed to insulin dependent diabetes mellitus ("IDDM", a.k.a. Type I diabetes), it is not a model of all other autoimmune disorders or even all "diabetes" type disorders, such as non-insulin dependent diabetes mellitus ("NIDDM", a.k.a. Type II diabetes).

For example a main characteristics of diabetes pathology in both human type I diabetes patients and *non-obese* diabetic mice is the CD8 insulin autoreactive T cell destruction of islets. However, this does not occur in patients predisposed to NIDDM (see The Merck Manual of Diagnosis and Therapy, Mark Beers and Robert Berkow, eds., Published by Merck Research Laboratories, 17th ed., 1999, pages 165-171, see in particular Table 13-1). Rather, patients predisposed to NIDDM have genetic predispositions to impaired insulin secretion and are obese which predisposes them to insulin resistance (see, Gerich et al., MedGenMed. 2004 Aug 26;6(3 Suppl):11, in particular page 3, 2nd paragraph).

As another example, in Celiac disease the cells responsible for turning a staple of the human diet - gluten - into a disease inducing antigen are the HLA-DQ2 and HLA-DQ8 gluten binding antigen presenting cells that, in turn, activate CD4+ Th1 and Th2 cells leading to inflammation and autoantibody production (see Schuppan, Gastroenterology. 2000 Jul;119(1):234-42, in particular Table 1, page 235, right column, 1st paragraph, page 236, left column, 2nd paragraph and Figure 4). In contrast, there is no well-recognized role for CD8+ T cells in Celiac disease.

Likewise, in a mouse colitis model, CD4+CD45RB^{high} T cells were capable of transferring the disease to recipient mice but CD8+ T cells were not (see Aranda et al., J Immunol. 1997 Apr 1;158(7):3464-73, in particular, Abstract).

As a further example, in lupus the cell responsible for producing anti-DNA antibodies is a B cell as well as the autoreactive CD4 T cell clones that support polyclonal antibody production (see Rajagopalan et al., PNAS 1990, Vol. 87, p. 7020-7024). Thus a showing that TNF-alpha kills autoreactive CD8 T cells in type 1 diabetes may not necessarily lead the skilled artisan to a conclusion that autoreactive B cells and CD4 T cells would be killed due to administration of TNF-alpha in a lupus patient.

Thus, the skilled artisan would have been unable to extrapolate the findings provided in Ban's manuscript to conclude that any autoimmune diseases could be positively treated with TNF-α. The skilled artisan would be required to conduct an undue amount of experimentation in order to conclude that administration of TNF-α in humans would positively treat lupus erythematosis, rheumatoid arthritis, multiple sclerosis, scleroderma, Crohn's disease, Grave's disease, psoriasis, Celiac disease, adult-onset idiopathic hypoparathyroidism (AOIH), Sjogren's syndrome, or Addison's disease.

Lastly, it is important to emphasize that the substantive experimental disclosure of the instant specification shows that spleen cells obtained from NOD mice undergo apoptosis when stimulated with TNF-α as compared to wild type cells as a consequence of defect in the NOD mice spleen cell in producing the "active" signaling form of NFKB due a defect in the NOD mouse proteosome (see instant specification page 124, lines 20-22; page 126, line 5 through page 127, line 6 and Figures 13A-13D). This is far from sufficient to enable the skilled artisan to treat the various autoimmune diseases encompassed by the breadth of the instant claims which have diverse etiologies and mechanisms of pathogenesis relative to type I diabetes.

The issue is make and use, not attempt to make and then test to see if the skilled artisan could use. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Furthermore, Fisher teaches "[t]he amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). This is because it is not obvious from the disclosure of one particular species, what other species will work, and if little is known in the prior art about the nature of the invention and the art is unpredictable, as in the instant case, the specification would need more detail as to how to make and use the invention in order to be enabling. See MPEP 2164.03.

As discussed above undue experimentation would be required to practice the claimed

invention commensurate with the scope of the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Thus, when Applicant's arguments and objective evidence are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain non-enabled in view of the nature of the invention and the state and unpredictability of the art. See M.P.E.P. § 716.01(d).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 76 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (U.S. Patent No. 5,370,870).

Wong teaches treating diabetes and other autoimmune diseases by a method comprising administering TNFα (see Wong column 4, 4th and 8th paragraphs; column 8 and claims 1 and 2).

Thus, Wong anticipates the instant claims.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Grewal et al., J Exp Med. 1996 Nov 1;184(5):1963-74, teaches as much as previously cited Jacob et al., Proc Natl Acad Sci U S A. 1990 Feb;87(3):968-72, which was the basis for a previous rejection under 35 U.S.C. § 102(b). The Jacob rejection was withdrawn in view of applicant's amendment to the claims to recite "human patient".

However, the teachings of Grewal go beyond those of Jacob in that Grewal demonstrates, for example, that NOD mice made transgenic for TNFα production under the control of a pancreas specific promoter (the rat insulin promoter, "RIP," used to a make "RIP-TNFα" transgenic mice) which locally express TNFα in their islets starting at 7 weeks are 1. less likely to become diabetic 2. have splenic T cells which are not autoreactive with an autoimmune peptide from the NOD model (GADp524-543) or with islet extract as are normal NOD splenic T cells and 3. have splenic T cells unable to adoptively transfer diabetes to recipient mice in contrast to normal NOD splenic T cells.

Nevertheless, Grewal does not mention treatment of human IDDM with TNFα and it would not be obvious to do so given the teachings of Grewal concerning the mechanisms of TNFα prevention of diabetes in the NOD mouse: Grewal hypothesizes that the mechanism of TNFα prevention of diabetes depends either on a TNFα mediated education of naïve T cells so that they are rendered anergic or deleted, or on a TNFα protective effect on islets, both seemingly requiring long term administration of TNFα before symptoms of disease occur (see last page of Grewal). This teaching in combination with the well known in the art pro-inflammatory effects of TNFα in humans would not have motivated one of ordinary skill in the art to treat a human exhibiting symptoms of IDDM with TNFα.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
September 25, 2008

/Eileen B. O'Hara/
Supervisory Patent Examiner
Art Unit 1644